

Postoperative Cognitive Decline

Where Art Tau?

TAU is an axonal microtubule-associated protein whose best known function is to bind and stabilize microtubules and promote their polymerization. Tau, a variously sized protein, has a number of repeated domains that bind tubulin and a number of phosphorylation sites that modulate its affinity for tubulin. In general, phosphorylation through a number of kinases decreases tau affinity to microtubules, whereas phosphatase activity dephosphorylates and increases affinity, resulting in tubulin binding and microtubule stabilization.¹

In Alzheimer disease and other tauopathies, tau becomes abnormally hyperphosphorylated and self-assembles into a number of higher-order structures, resulting in fibrillar-paired helical filaments, the core components of the classic intracellular neurofibrillary tangles.² How hyperphosphorylated tau, paired helical filaments, or neurofibrillary tangles go on to cause or contribute to cellular and synaptic dysfunction is not entirely clear,³ but the correlation with the ultimate cognitive deficits is better than with other neuropathologic lesions, such as the amyloid plaque.^{4,5}

That the state of anesthesia can result in tau hyperphosphorylation was sprung on us a few years ago by Planel *et al.*,⁶ but we breathed a collective sigh of relief when it was carefully demonstrated that anesthesia-associated hypothermia was the culprit, rather than the drug itself, and that the effects were quickly reversible. The article in this month's ANESTHESIOLOGY by Le Freche *et al.* suggests we may have relaxed too soon.⁷

Le Freche *et al.* exposed wild type mice to two concentrations of sevoflurane for 1 h once a month for 5 months starting at 5 months of age. There was no surgery. Immediately after the first exposure, phosphorylated tau was increased in the brain but not after 24 h. However, sometime between this first exposure and the fifth exposure, the effect on phosphorylated tau concentrations in the brain were no



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longer transient. A full month after the last exposure, phosphorylated tau in the hippocampus was increased dramatically, and the putative responsible kinases were identified. This is of interest because hypothermia-associated elevations in phosphorylated tau were associated with decreases in phosphatase activity, rather than activation of kinases. In addition, anesthetics may directly bind to and alter tubulin, promoting both tau release and microtubule dysfunction.⁸ Thus, although this area remains understudied, anesthesia and its associated physiology might produce multiple hits on the tau and tubulin pathway.

The work by Le Freche *et al.* is not the first time that persistent changes in tau have been identified after anesthesia. Elevations in insoluble tau and phosphorylated tau were found weeks to months

after isoflurane anesthesia in mouse models of either tauopathy or Alzheimer disease.^{9,10} Moreover, there is evidence for translation to humans. Tang *et al.* found increased tau and phosphorylated tau in the cerebrospinal fluid of patients as long as 48 h after endoscopic surgery with propofol/remifentanyl or sevoflurane anesthesia,¹¹ and Palotás *et al.*, found increased total tau as long as 6 months after coronary artery bypass graft surgery performed during total intravenous anesthesia.¹² Although it is impossible to determine causality in these early clinical studies, it seems that a case for perioperative modulation of tau is emerging.

So what? Tau is modulated physiologically. For example, phosphorylated tau is increased during fetal and neonatal development, where it is thought to contribute to the less-stable neuronal cytoskeleton required in periods of neuronal growth and plasticity.¹³ Le Freche *et al.* anticipate this question by performing cognitive studies on their mice between the fourth and fifth sevoflurane exposures. Using the Morris water maze, they find that working memory is not different

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from that of controls, but memory retention is diminished significantly in the sevoflurane-exposed animals.

Unlike the researchers of the human studies, Le Freche *et al.* are able to link the anesthetic alone with both phosphorylated tau and memory effects. But as with the human studies, they are unable to make the link between phosphorylated tau and the memory effects. At this point, it is simply an intriguing association, but it allows the hypothesis that tau and perhaps microtubule dysfunction may underlie altered cognition after surgery. Direct tests of this idea are possible in animals, such as in tau knockout mice, but would be difficult in humans. Perhaps searching for parallel rank order effects of different anesthetics might allow some linkage, as might pre- or cotreatment with a variety of compounds that stabilize microtubules. The small molecule Epopilone D and the octapeptide NAPVSIPQ are examples of microtubule-stabilizing compounds that delay onset of pathology and symptoms in neurodegenerative animal models and soon will be entering clinical Alzheimer trials.^{14,15} It would be interesting if such drugs found a place in perioperative medicine in the future.

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